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09/957,031	09/21/2001	David Margolis	BSZ-008DV	6530

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EXAMINER	
SULLIVAN, DANIEL M	
ART UNIT	**PAPER NUMBER**
1636	16

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/957,031	MARGOLIS ET AL.	
	Examiner	Art Unit	
	Daniel M Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 May 2003 and 05 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *89-190* is/are pending in the application.

4a) Of the above claim(s) *101-108,129-136 and 161-168* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *89-100,109-128,137,140-145,148-160 and 169-190* is/are rejected.

7)☒ Claim(s) *138,139,146 and 147* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This Non-Final Office Action is a reply to the "Response" filed 5 May 2003 (Paper No. 13) and "Supplemental Response" filed 5 August 2003 (Paper No. 15) in response to the Non-Final Office Action mailed 5 November 2002 (Paper No. 9). Claims 101-108, 129-136 and 161-168 were withdrawn from consideration and claims 89-100, 109-128, 137-160 and 169-190 were considered in Paper No. 9. Claims 89-190 are pending and claims 89-100, 109-128, 137-160 and 169-190 are under consideration.

Response to Arguments

Claim Rejections - 35 USC § 112

Rejection of claims 89-100, 109-116 and 179-187 under 35 U.S.C. §112, first paragraph, as lacking enablement for the full scope of the claims is withdrawn. As the claims are enabled for *in vitro* use, the full scope of the product claims has enabled utility.

Claims 140, 148-160, 169-178 and 188-190 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *in vitro* applications, does not reasonably provide enablement for *in vivo* use for reasons of record. Unlike the product claims, the method claims drawn to *ex vivo* therapeutic application encompass many embodiments that are not enabled by the teachings in the specification for reasons set forth in the previous Office Action.

In response to the rejection of record, Applicant alleges that the claims are not directed to gene therapy generally. Applicant asserts that any generalization as to the state of the gene

therapy art does not apply to the claimed subject matter in view of the significant advances made in gene therapy using cochleate technology and in view of successful gene therapy protocols. It should first be made clear that the Examiner disagrees with Applicant's assertion that the claims are not directed to gene therapy generally. The method claims are directed to the *ex vivo* treatment of a subject and recite broad method steps that would be common to the treatment any condition. The claims are not limited to treatment of any specific disease or condition. Furthermore, the products used in the method are not limited to comprising any particular therapeutic ingredient, or in some embodiments contemplate a variety of therapeutic ingredients that would be used to treat widely divergent pathologies. Thus, the methods are directed to treating essentially any disease or condition according to the general method steps set forth in the claims. Contrary to Applicant's assertion, the claims are in fact very broad, and generally encompass a method of treating any condition using an *ex vivo* approach. As the claims must be enabled for their full scope (see, e.g., *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Goodman*, 11 F.3d 1046, 1052, 29 USPQ2d 2010, 2015 (Fed. Cir. 1993); *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); and *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991), the disclosure must provide teachings that support the broad claims, or the claims must be limited to a scope that is enabled by the disclosure. However, in the instant case, the disclosure does not provide a single enabled embodiment of an *ex vivo* method.

To support the alleged enablement of the claims, Applicant cites several teachings from the gene therapy art, which will be addressed in the order they are presented. It should first be pointed out that many of the cited references were published after the effective filing date of the

instant application and therefore are only relevant to the present discussion insofar as they provide a retrospective view of the state of the art 14 December 1998, the date that the parent application was filed.

First, Applicant cites several articles indicating showing that *in vivo* administration of nucleic acids encoding immunogenic polypeptides can elicit an immune response in experimental animals (i.e., Gould-Fogerite *et al.* (1998) *Advanced Drug Deliver Reviews* 32:273-287; Mannino & Gould-Fogerite (1997) *New Gen. Vaccines*, Chapter 18, pp. 229-237 (Marcel Dekker 2d Ed.); Gould-Fogerite & Mannino (1999) *Meth. Mol. Med.* 42:179-197; and Michalek *et al.* (1999) *Mucosal Immunol.* Chapter 47, pp. 759-778 (Academic Press)). However, even assuming *arguendo* that methods for eliciting an immune response comprising *in vivo* administration of nucleic acids is fully enabled, the instant claims are not limited to methods for eliciting an immune response or to delivering nucleic acids that would produce a useful immune response. In fact, in the case of some of the specific embodiments of the claimed invention, such as delivery of adenosine deaminase, an immune response against the delivered protein would be an obstacle to achieving a successful therapeutic result. Furthermore, with respect to enablement for an *ex vivo* method of vaccination, the teachings of the cited art deals exclusively with *in vivo* methods and therefore does not provide critical guidance, such as effective dosage and route of administration, for using the instant claimed *ex vivo* method to elicit an immune response.

Applicant cites Parker *et al.* (1999) *Methods Enzyme.* 313:4111-429 as demonstrating enablement for the method. Parker *et al.* teaches that systemic delivery of a phosphorothioate-derivatized IL-10 antisense oligonucleotide suppresses growth of an IL-10 dependent malignant cell line *in vivo*. The method of Parker *et al.* is not analogous to the instant claimed method: first,

because the nucleic acids are delivered systemically *in vivo*, not *ex vivo*; and second, because the method does not require expression of the delivered nucleic acid in the cell. The fundamental problem encountered in establishing any effective gene therapy is achieving a therapeutic level and duration of transgene expression. Parker *et al.* circumvents this problem by delivering a nucleic acid that does not require expression for efficacy. However, the instant claims are directed to delivering nucleic acids *ex vivo* and encompass methods of treatment that require expression of nucleic acids in the cells that take up the nucleic acid. For reasons provided in the previous office action, obtaining therapeutic expression via an *ex vivo* method is unpredictable. Parker *et al.* side steps the limitations of expression, in a way that would not be possible for the instant claimed method, by delivering the nucleic acid *in vivo* and in a directly active form. Therefore, Parker *et al.* fails to teach how to overcome the barriers facing the skilled artisan seeking to practice the full scope of the claimed invention.

Applicant cites Brenner *et al.* (1994) *Ann. NY Acad. Sci.* 716:204-215 and Kiem *et al.* (1995) *Curr. Opin. Oncol.* 7:107-114 as demonstrating that *in vitro* manipulation of hematopoietic stem cells is well known to those of ordinary skill in the art. However, although Brenner *et al.* and Kiem *et al.* teach that *ex vivo* gene transfer can be used to mark cells used in autologous bone marrow transplant, the authors agree, contrary to Applicant's assertions, that obtaining sufficient expression for therapeutic application is not enabled. Brenner *et al.* teaches, "most early large animal models suggested that it would be difficult to transduce novel genes into a significant proportion of marrow stem cells and to express the gene in their progeny" (paragraph bridging pages 204 and 205) and suggests only that the methods disclosed might be enabled as a method of following bone marrow cells after transplantation. Kiem *et al.* plainly

teaches, "[c]urrent transduction efficiency of hematopoietic stem cell in large animals and humans appears to be sufficiently high...for gene marking studies. Efficiency needs to be further increased before gene transfer can be used for therapeutic applications" (abstract). Clearly the instant claims are not limited to a method that would be enabled by the teachings of Brenner *et al.* or Kiem *et al.* (i.e., gene marking) and neither Brenner *et al.* or Kiem *et al.* address the problems of obtaining sufficient level and duration of expression for therapeutic use that would enable the full scope of the instant claims.

Applicant next cites Cavazana-Calvo *et al.* (2000) *Science* 288 :669-672 as evidence that manipulation of hematopoietic stem cells, taken from an animal or human patient, and the affect of autologously transplanting these manipulated cells has been widely practiced and reported. Cavazana-Calvo *et al.* teaches treatment of SCID-X1 comprising transfer of a γc transgene into T lymphocytes. However, even assuming *arguendo* that the treatment of SCID according to the method Cavazana-Calvo *et al.* is fully enabled, the instant claims are not limited to a method of treating SCID-X1 and do not teach or suggest administering a γc gene into T-lymphocytes. Furthermore, the teachings of Cavazana-Calvo *et al.* do not suggest enablement for any scope beyond treatment of SCID-X1 comprising administering the γc gene into T-lymphocytes. In the methods of Cavazana-Calvo *et al.*, correction of the genetic defect is targeted directly to the affected cells and provides a selective survival advantage for those cells. The art recognizes that relative success obtained in treatment of SCID using genetically modified T cells is probably due to the selective advantage provided the genetically modified cells by correction of the defective gene therein. Somia *et al.* (2000) *Nature Rev. Genet.* 1:91-99, commenting on the findings of Cavazana-Calvo *et al.*, states, "the success with SCID-X1 is probably owing to the strong

selective advantage provided to the transduced lymphoid progenitors. Only those haemtaopoietic cells that express the γc receptor subunit can survive and differentiate" (page 96, column 1). In contrast, the instant invention encompasses many embodiments wherein the genetically modified cells would not have the selective advantage credited for the relative success of treatment of SCID-X1, and which are therefore not enabled by the teachings of Cavazana-Calvo *et al.*

Applicant cites Schiedlmeier *et al.* (2000) *Blood* 95:1237-1248 as teaching successful *ex vivo* gene therapy using human CD34+ cells transduced with retroviral-mediated cytostatic drug resistance genes. However, contrary to Applicant's assertion, Schiedlmeier does not teach a therapeutic method but, in the words of Schiedlmeier *et al.*, "a valid assay for estimating the gene-transfer efficiency to repopulating human PBPC that may be achievable in clinical autologous transplantation" (abstract, emphasis added). In fact, Schiedlmeier *et al.*, which was published two years after the effective filing date of the instant application, cites articles published as late as 1998 as evidence that "*MDR1*-mediated chemoprotection in large animals or in human gene-therapy trials has been hampered by a low number of reconstituting vector-marked cells and inefficient expression of the transgene *in vivo*, despite high levels of gene transfer into HPC and long-term culture-initiating cells" (paragraph bridging columns 1 and 2 on page 1237). Thus, even if Schiedlmeier *et al.* disclosed a gene therapy method that was enabled in the year 2000, which it does not, the authors teach that methods of gene therapy by *MDR1*-mediated chemoprotection were not enabled at the time the instant application was filed.

Applicant cites Parkman *et al.* (2000) *Annual Rev. Med.* 51:33-57 as evidence for enablement for gene therapy of adenosine deaminase deficiency. Again, even assuming *arguendo* that the teachings of Parkman *et al.* demonstrated full enablement for a method of

treating adenosine deaminase deficiency at the time the instant application was filed, the claims are not limited to treating adenosine deaminase deficiency or to delivering transgenes that would have any therapeutic value in the treatment of adenosine deaminase deficiency. Furthermore, contrary to Applicant's assertion, Parkman *et al.* teaches that gene therapy of adenosine deaminase deficiency and gene therapy in general remained problematic and lacked enablement even two years after the effective filing date of the instant application. Importantly, Parkman *et al.* teaches, "attempts to teat ADA deficiency define the status of gene therapy and illustrate the limitations that will have to be overcome before it can become an established treatment for ADA deficiency and other genetic diseases" (paragraph bridging pages 33 and 34). Thus, Parkman *et al.* teaches that, at least with respect to genetic diseases, limitations remained to be overcome before gene therapy would be considered enabled. Parkman *et al.* goes on to teach, "[i]f gene therapy is to become an established curative therapy for ADA deficiency or any other monozygotic genetic disease, it is necessary (a) to generate vectors capable of supporting appropriate gene expression and (b) to increase the frequency of human HSC transduction" (final paragraph on page 38). Thus Parkman *et al.* teaches that gene therapy was not considered an established curative therapy for any monozygotic genetic disease as of the year 2000 and cites gene expression as one of the two important hurdles remaining to be overcome. Finally, Parkman *et al.* teaches that significant experimentation remains to be done before gene therapy of primary lymphoid immunodeficiency disorders is enabled, "gene therapy for ADA deficiency give[s] promise but also define[s] the present limitations of gene therapy for primary lymphoid immunodeficiency disorders...the lack of gene expression in nondividing T lymphocytes resulted in lack of persisting transduced T lymphocytes when an exogenous source of ADA was

curtailed. To permit gene therapy to successfully treat diseases of lymphoid differentiation, vectors that are expressed in mature, nondividing lymphoid cells will be necessary. The successful treatment of diseases of function will require approaches that increase the frequency of stable HSC transduction and result in appropriate gene expression" (page 44)

Applicant cites Isner *et al.* (1999) *J. Clin. Invest.* 35 U.S.C. §103:1231-1236 as demonstrating that CD34+ cells can appropriately populate and differentiate into endothelial cells when transplanted *ex vivo.* However, the basis for the enablement rejection is that the skilled artisan would not be able to obtain therapeutic levels and duration of transgene expression using the instant claimed method without the need for undue additional experimentation. Isner *et al.* does not teach engraftment of genetically modified cells or the use of genetically modified cells to obtain a therapeutic effect. Therefore, the teachings of Isner *et al.* do not address the grounds for the present rejection.

Likewise, the citations in the first and second full paragraphs on page 4 of Paper No. 13, which allegedly demonstrate that cochleates can be administered safely and deliver drugs into cells do not speak to the difficulties encountered in obtaining therapeutic transgene expression, which is the basis for lack of enablement.

Applicant states, "studies demonstrating the successful *in vivo* delivery of biologically active molecules in cochleates, and the use of CD34+ cells *in vivo* to achieve gene therapy, reasonably allows the extrapolation of Applicants' *in vitro* data to gene therapy applications" (sentence bridging pages 4-5). However, for reasons set forth above, the art of record does not indicate that the instant methods are enabled for any particular embodiment, let alone the broad

scope encompassed by the claims. Therefore, the claims stand rejected as lacking an enabling disclosure.

Double Patenting

Claims 89-100 and 109-116 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-28 of U.S. Patent No. 6,340,591. Applicant's statement regarding the filing of a terminal disclaimer upon allowance of the conflicting claims in Paper No. 13 is acknowledged and the double patenting rejection will be withdrawn upon receipt of the terminal disclaimer.

Claim Rejections - 35 USC § 103

Claims 89-99, 109, 111-115, 117-127, 137, 140-145, 148-159, 169, 172-176, 182-184 and 189 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Wiener *et al.* (U.S. Patent 6,342,390, filed November 23, 1994) in view of Mannino and Gould-Fogerite (1996; WO 96/25942).

In response to the rejection of record, Applicant argues that the disclosure of the advantages of cochleates provided in Mannino provides neither the motivation nor a reasonable expectation of success, particularly in view of the marked differences between liposomes and the cochleates of Mannino. Applicant provides a summary of *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991) and states, "[s]imilar to *In re Vaeck*, there is no disclosure or suggestion in either cited reference to modify Weiner to realize the claimed invention. Contrary to the assertion in the outstanding Office Action, the recitation of advantages of cochleates as vehicles for delivery of

biologically active materials in Mannino provides neither the suggestion nor the motivation to combine the references required to establish obviousness" (bridging pages 6-7) and "cochleates and liposomes are not considered to be interchangeable at least because cochleates and liposomes have fundamentally different structures, properties an delivery mechanisms" (page 7, first full paragraph). Applicant then points out several structural and functional differences between liposomes and cochleates. Applicant states, "it was not known prior to Applicants' invention, whether the claimed combination would be successful" (page 8, second full paragraph).

These arguments have been fully considered but are not found persuasive. With respect to a suggestion to combine the references, Mannino *et al.* clearly states that cochleates can be used to deliver nucleic acids into cells (see especially page 3, lines 4-5 and lines 19-28). Furthermore, Mannino *et al.* explicitly teaches that cochleates are superior to liposomes in many ways (see especially page 4, line 12 through page 5, line 27). Thus, unlike in *In re Vaeck*, the art in the instant case explicitly teaches that cochleates can be applied to the same purpose as liposomes and that cochleates are superior to liposomes. Thus, the teachings of Mannino *et al.* clearly suggest substitution of cochleates for liposomes, particularly for delivery of therapeutic molecules and nucleic acids.

With regard to the expectation of success, it should be pointed out that Mannino *et al.* is Applicant's own disclosure. Therefore, the statement made in the instant "Response" (i.e., that it was not known whether the claimed combination would be successful prior to Applicant's invention) appears to directly contradict Applicant's own statements made in Mannino *et al.* and claims (e.g., claim 14) published two years before the instant application was filed. Mannino *et*

al. clearly teaches that cochleates can be used to deliver nucleic acids into cells and Applicant has provided no evidence that would undermine this assertion. Therefore, one of ordinary skill in the art would have a reasonable expectation of success in combining the teachings of Mannino *et al.* with the teachings of Weiner *et al.* according to the instant claimed invention.

Applicant's arguments have been fully considered but are not found persuasive either individually or as a whole; therefore, the claims stand rejected as obvious over Weiner *et al.* in view of Mannino *et al.*

New Grounds for Rejection

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 100, 128, 160, 179-181 and 185-188 and 190 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wiener *et al.* (U.S. Patent 6,342,390, filed November 23, 1994) in view of Mannino *et al.* (1996; WO 96/25942).

Although the rejection set forth in the previous Office Action was not applied to the claims, upon further review, it is clear that they are obvious over the cited art. Claims 100, 128 and 160 are drawn to the compositions and methods of claims 94, 122 and 154, respectively, wherein the binding protein is an integrase and at least one of the one or more DNA sequences recognized and bound by the one or more binding proteins is a substrate for said integrase. As described in the previous Office Action and herein above, Wiener *et al.* and Mannino *et al.* teach all of the limitations of claim 94, 122 and 154, provide motivation to combine the teachings to

produce the instant claimed invention and a reasonable expectation of success. Furthermore, as pointed out in the previous office action, Weiner *et al.* teaches a method and composition comprising the AAV rep 68 and rep 78 DNA binding proteins. As the instant specification indicates that rep 68 and 78 mediate complex formation between AAV DNA and its integration site and possess helicase and site specific endonuclease activities that facilitate integration of AAV (see especially the third full paragraph on page 5), helicase activity is inherent to the rep 68 and rep 78 proteins taught by Mannino *et al.* Therefore, the limitations of claims 100, 128 and 160 would be obvious to one of ordinary skill in the art at the time the invention was made for the reasons set forth in the previous Office Action and herein above regarding claims 94, 122 and 154.

Claims 179-181 and 188 are directed to the same vector delivery structures and methods demonstrated in the previous Office Action and herein above to be obvious over Wiener *et al.* and Mannino *et al.*, wherein the nucleotide sequence that expresses a molecule is further limited to a normal gene for adenosine deaminase. As, Wiener *et al.* teaches that the compositions and methods described therein can comprise a DNA sequence encoding adenosine deaminase (see especially column 4), all of the limitations of claims 179-188 are disclosed in Wiener *et al.* and Mannino *et al.* and would be obvious to one of ordinary skill in the art at the time the invention was made for the reasons set forth in the previous Office Action and herein above.

Claims 185-187 and 190 are also directed to the same vector delivery structures and methods demonstrated in the previous Office Action and herein above to be obvious over Wiener *et al.* and Mannino *et al.*, wherein the nucleotide sequence that expresses a molecule is a normal surface receptor. As, Wiener *et al.* teaches that the compositions and methods described therein

can comprise a DNA sequence encoding a T-cell receptor and Fc receptors (see especially column 4), all of the limitations of claims 185-187 and 190 are disclosed in Wiener *et al.* and Mannino *et al.* and would be obvious to one of ordinary skill in the art at the time the invention was made for the reasons set forth in the previous Office Action and herein above.

Thus, the instant claims 179-181 and 185-188 and 190 as a whole would be *prima facie* obvious to one of ordinary skill in the art at the time the application was filed.

Allowable Subject Matter

Claims 138, 139, 146 and 147 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 703-305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

DMS

JAMES KETTER
PRIMARY EXAMINER